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EXAMINER	
ARIANI, KADE	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,678	HU ET AL.	
	Examiner	Art Unit	
	KADE ARIANI	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☒ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on August 29, 2008, has been received and entered.

Claims 1-47 are pending in this application and were examined on their merits.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/29/2008 has been entered.

Claim Objection

Claim 29 is objected to because of the following informalities:

The word --gelation—in claim 29 (last line) is misspelled as "gelationin".

Appropriate correction is required.

Applicant's arguments with respect to claims 1-47 filed on 08/29/2008 have been fully considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 11-13 under 35 U.S.C. 112, second paragraph is withdrawn due to Applicants amendments to the claims filed on 08/29/2008.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102(b) that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicant's arguments with respect to the rejection of Claims 1, 4-10, and 13-14 under 35 U.S.C. 102(b) as being anticipated by Dhara et al. (Macromol Chem. Phys. 2001, Vol. 202, p.3617-3623) have been considered and are persuasive, therefore the rejection is withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15, 20-22, 24-26, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Bouillot et al. (Colloid Polym Sci, 2000, Vol. 278, p.74-79).

Claims 15, 20-22, 24-26, and 28 are drawn to a method of preparing an interpenetrating polymer network (IPN) of monodispersed nanoparticles, comprising, providing a first mono-dispersed polymer nanoparticles prepared by mixing first monomer, a surfactant, a first cross linking agent, and first initiator at a first temperature, adding to the first mono-dispersed polymer nanoparticles a second monomer, a second cross linking agent, a second initiator and an activator, mixing the nanoparticles solution for a period of time at a second temperature to form the IPN on mono-dispersed nanoparticles, isolating the IPN nanoparticles, wherein the first monomer, the first cross linking agent, the second monomer, and the second cross linking agent are substantially free from dissolved oxygen gas and the first wherein the first polymer forms a first polymer network which interpenetrates a second polymer network formed by the second polymer, wherein the first polymer comprises poly (-N-isopropylacrylamide) and the second polymer comprises poly (acrylic acid),

hydrodynamic radius in the range of 75 nm to about 200 nm, period of time is less than 130 minutes and is about 120 minutes, and the second temperature at about 21°C.

Bouillot et al. disclose a method of preparing an interpenetrating polymer network (IPN) of monodispersed nanoparticles (p.76 1st 2nd column 1st paragraph lines 5-8), comprising, providing a first mono-dispersed polymer nanoparticles prepared by mixing first monomer, a surfactant, a first cross linking agent, and first initiator at a first temperature, adding to the first mono-dispersed polymer nanoparticles a second monomer, a second cross linking agent, a second initiator and an activator, mixing the nanoparticles solution for a period of time at a second temperature to form the IPN on mono-dispersed nanoparticles, wherein the first polymer comprises poly (-N-isopropylacrylamide) and the second polymer comprises poly (acrylic acid), isolating the IPN nanoparticles, wherein the first monomer, the first cross linking agent, the second monomer, and the second cross linking agent are substantially free from dissolved oxygen gas (solutions purged with N_2), period of time is less than 130 minutes and is about 120 minutes, and the second temperature is 25°C (about 21°C)(p.75 2nd column 2nd and 3rd paragraphs), and the first wherein the first polymer forms a first polymer network which interpenetrates a second polymer network formed by the second polymer (p.78 1st column 1st paragraph), hydrodynamic diameter (radius) is 150 nm (in the range of 75 nm to about 200 nm) (p.76 1st column last paragraph lines 10-11).

Bouillot et al. therefore clearly anticipate the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouillot et al. (Colloid Polym Sci, 2000, Vol. 278, p.74-79) in view of Qiu et al. (Advanced Drug Delivery, 2001, Vol. 53, p.321-339) and further in view of over Cai et al. (Journal of Applied Polymer Science, 2002, Vol. 83, p.169-178) and further in view of Jeong et al. (Advanced Drug Delivery Reviews, 2002, Vol. 54, p.37-51).

Claims 1-14 are drawn to an aqueous dispersion of hydrogel nanoparticles comprising, interpenetrating polymer network (IPN) nanoparticles, wherein each IPN nanoparticles comprises a first polymer network interpenetrating a second polymer network, and an aqueous medium, wherein the IPN nanoparticles are substantially free of shell and core polymer configuration, and the aqueous dispersion of hydrogel nanoparticles can undergo a reversible gelation in response to a change in stimulus applied thereon, the aqueous dispersion of hydrogel nanoparticles further comprising a biologically active material, wherein the stimulus comprises a change in temperature, Tg is about 34ºC, poly (-N-isopropylacrylamide) and the second polymer comprises poly (acrylic acid), a uniformed sized hydrodynamic radius in the range of 75 nm to about

200 nm, IPN nanoparticles have weight ratio of about 1:1.88, and total polymer concentration from about 1.25 wt% to about 5.25 wt% in distilled water.

As mentioned immediately above, Bouillot et al. teach a method of preparing an interpenetrating polymer network (IPN) of monodispersed nanoparticles (p.76 1st 2nd column 1st paragraph lines 5-8). Bouillot et al. teach IPN particles containing various acrylic acid/acrylamide (AAc/AAm) ratios and different cross-linker amounts, were prepared (p.75 1st column 4th paragraph). Bouillot et al. further teach thermosensitive IPN hydrogels have been synthesized that could be used for control drug release. Bouillot et al. teach the principle of controlled drug release, using ketoprofen as the drug, from PAAc/PAAm IPN hydrogels in response to a temperature (p.75 1st column 2nd paragraph), hydrodynamic diameter (radius) is 150 nm (in the range of 75 nm to about 200 nm) (p.76 1st column last paragraph lines 10-11).

Bouillot et al. do not teach wherein…the aqueous dispersion of hydrogel nanoparticles can undergo a reversible gelation in response to a change in stimulus applied thereon, wherein a temperature change above a gelation temperature (Tg) induces a volume phase transition resulting in an inverse thermo-thickening property of the aqueous dispersion of the hydrogel nanoparticles, Tg is about 34ºC, weight ratio of about 1:1.88, and total polymer concentration from about 1.25 wt% to about 5.25 wt% in distilled water. However, Qiu et al. teach if the polymer chains in hydrogels are not covalently cross-linked, temperature-sensitive hydrogels may undergo sol-gel phase transitions instead of swelling-shrinking transitions. The thermally reversible gels with inverse temperature dependence become sol at higher temperatures. Qiu et al. teach

temperature-sensitive hydrogels can also be made using temperature sensitive cross-linking agents (p.324 2nd column 1st and 2nd paragraphs). Qiu et al. further teach as the polymer chain which contains more hydrophobic constituents, LCST becomes lower, and the LCST can be changed by adjusting the ratio of hydrophilic and hydrophobic segment of the polymer (p.324 1st column lines 8-12).

Further motivation is in Cai et al. who teach Inside IPN hydrogels, each network may retain its own properties, whereas the proportions of the networks are varied independently. The combined properties of the IPNs can be controlled by the ratios of their component monomers (p.170, 2nd column 2nd paragraph). Cai et al. teach poly (-N-isopropylacrylamide) hydrogels undergoes a reversible volume phase transition at 32ºC (LCST)(p.169 1st column lines 10-14).

Even further motivation is in Jeong et al. who teach an aqueous solution of NiPAAM/acrylic acid copolymer showed reversible gelation above a critical concentration around 32ºC rather than polymer precipitation (p.40 2nd column 2nd paragraph). Jeong et al. teach above the critical concentration (critical gel concentration CGC) of a polymer, the gel phase appears. The CGC is most often inversely related to the molecular weight of the polymer employed. The development of physical junctions in the system is regarded as one of the prerequisites in determining gelation. The determination of the boundary between the sol and gel phases depends on the experimental method. A simple test-tube inverting method was employed to roughly determine the phase boundary. When a test tube containing a solution is tilted, it is defined as a sol phase if the solution deforms by flow, or a gel phase if there is no flow.

The flow is a function of time, tilting rate amount of solution, and the diameter of the test tube (p.38 1st column 2nd and 3rd paragraphs).

Therefore, in view of the above teachings, a person of ordinary skill in the art at the time the time the invention was made could have been motivated to modify the method as taught by Bouillot et al. by changing the weight ratio of the first and second polymer and total polymer concentration in order to obtain an aqueous dispersion of hydrogel nanoparticles comprising, interpenetrating polymer network (IPN) nanoparticles, with predictable results. All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. KSR, 550 U.S. at ___, 82 USPQ2d at 1395; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson 's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).

Claims 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouillot et al. (Colloid Polym Sci, 2000, Vol. 278, p.74-79) in view of Kurisawa et al. (Journal of Controlled Release, 1998, Vol. 54, p.191-200) and further in view of Qiu et al. (Advanced Drug Delivery, 2001, Vol. 53, p.321-339).

Claims 15, 20-22, 24-26, and 28 are drawn to a method of preparing an IPN comprising, providing a first polymer nanoparticles prepared by mixing first monomer, a

surfactant, a first cross linking agent, and first initiator at a first temperature, adding to the first mono-dispersed polymer nanoparticles a second monomer, a second cross linking agent, a second initiator and an activator, mixing the nanoparticles solution for a period of time at a second temperature, isolating the IPN nanoparticles, mixing the isolated IPN with a biologically active material at a third temperature, poly (acrylic acid) (2^{nd} monomer), mixing for about 120 minutes at about 21°C (2^{nd} temperature), isolating the IPN, and mixing the isolated IPN with a biologically active material at a third temperature at about 33°C.

As mentioned immediately above, Bouillot et al. teach the limitations of claims 15, 20-22, 24-26, and 28. Bouillot et al. further teach thermosensitive IPN hydrogels have been synthesized that could be used for control drug release. Bouillot et al. teach the principle of controlled drug release, using ketoprofen as the drug, from PAAc/PAAm IPN hydrogels in response to a temperature (p.75 1^{st} column 2^{nd} paragraph).

Bouillot et al. do not teach the mixing the isolated IPN of mono-dispersed nanoparticles with a biologically active material at a third temperature, the third temperature is below a gelation temperature (Tg) of the IPN of mono-dispersed nanoparticles in an aqueous solution, and the Tg is about 33ºC. However, Kurisawa et al. teach a method of preparing an interpenetrating polymer network (IPN)-structured hydrogels of gelatin (Gtn) and dextran (Dex) with lipid microspheres (LMs) as a drug microreservoir (as a model of a drug substrate), the a phase morphology in the IPN-structured hydrogels was varied with the preparation temperature, i.e. above or below the sol-gel transition temperature (T_{trans}) of gelatin (Abstract, and p.194 2^{nd} column 1^{st}

paragraph). Kurisawa et al. teach the IPN-structured hydrogels were prepared below or above the T_{trans} of gelatin and their enzymatic degradability was examined. Dual-stimuli-responsive degradation was achieved in the IPN-structured hydrogels with Gtn and Dex networks that were prepared below T_{trans} having increased miscibility and the dual-stimuli-responsive degradation of Gtn-Dex hydrogels was closely related to the miscibility between Gtn and Dex networks (p.192, 1st column last paragraph and 2nd column 1st paragraph). Kurisawa et al. further teach regulated LM release was achieved in the IPN-structured hydrogel prepared below the T_{trans}, and although LM release from IPN-structured hydrogel prepared above the T_{trans} was observed, the difference in the LM release behavior is though to be have been caused by enzymatic degradability of the hydrogels, being closely related to physical chain entanglements between chemically different polymer networks (p.199 2nd column last paragraph, Conclusion).

Further motivation is in Qiu et al. who teach the common characteristics of temperature sensitive polymers is the presence of hydrophobic groups, and by using different monomers the lower critical solution temperature (LCST) of temperature-sensitive polymers can be altered (p.323 1st column last paragraph and 2nd column 1st paragraph). Qiu et al. further teach as the polymer chain which contains more hydrophobic constituents, LCST becomes lower, and the LCST can be changed by adjusting the ratio of hydrophilic and hydrophobic segment of the polymer (p.324 1st column lines 8-12). Qiu et al. teach if the polymer chains in hydrogels are not covalently cross-linked, temperature-sensitive hydrogels may undergo sol-gel phase transitions instead of swelling-shrinking transitions. The thermally reversible gels with inverse

temperature dependence become sol at higher temperatures. Qiu et al. teach temperature-sensitive hydrogels can also be made using temperature sensitive cross-linking agents (p.324 2nd column 1st and 2nd paragraphs). It must be noted that a polymer above the critical concentration (called critical gel concentration) the gel phase appears. Thus, a person of ordinary skill in the art at the time the invention was made would have recognized that gelation temperature (Tg) of IPN hydrogel is variable which is controlled by the hydrophobic interactions among the polymer chains.

Therefore, in view of the above teachings, a person of ordinary skill in the art at the time the invention was made could have been motivated to mix a the isolated IPN of mono-dispersed nanoparticles as taught by Bouillot et al. with a biologically active material at a temperature which is below the gelation temperature (Tg) of the IPN of mono-dispersed nanoparticles according to the teachings of Kurisawa et al. with predictable results. The motivation as taught by Kurisawa et al. would be able to regulate the release of the biologically active molecule.

Claims 15 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouillot et al. (Colloid Polym Sci, 2000, Vol. 278, p.74-79) in view of Jones et al. (Macromolecules, 2000, Vol. 33, p.8301-8306) and further in view of Soane (US Patent No. 5,135,627).

Claims 15 and 23 are drawn to a method of preparing an IPN comprising, providing a first polymer nanoparticles prepared by mixing first monomer, a surfactant, a first cross linking agent, and first initiator at a first temperature, adding to the first mono-

dispersed polymer nanoparticles a second monomer, a second cross linking agent, a second initiator and an activator, mixing the nanoparticles solution for a period of time at a second temperature, isolating the IPN nanoparticles, N, N'-methylenebisacrylamide, potassium persulfate, ammonium persulfate, the surfactant comprises SDS, and TEMED (activator).

As mentioned immediately above, Bouillot et al. teach the limitations of claim 15. Bouillot et al. further teach N, N'-methylenebisacrylamide (BIS), ammonium persulfate, and TEMED (p.75 1st column last paragraph and 2nd column 1st paragraph).

Bouillot et al. do not teach the surfactant comprises SDS and the initiator comprises potassium persulfate. However, Jones et al. teach synthesis of hydrogel nanoparticles using SDS (p.8301 2nd column 2nd paragraph).

Moreover, Soane teaches potassium persulfate may be substituted for ammonium persulfate as an initiator (column 6 lines 5-8).

Therefore, in view of the above teachings, a person of ordinary skill in the art at the time the invention was made, could have been motivated to modify the method as taught by Bouillot et al. by substituting the surfactant and the initiator with SDS and ammonium persulfate as taught by Jones et al. and Soane with predictable results. Because the substitution of one known surfactant and initiator with another known surfactant and initiator would have yielded predictable results to one of ordinary skill in the art at the time the invention was made.

Claims 15 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cai et al. (Journal of Applied Polymer Science, 2002, Vol. 83, p.169-178) in view of Bouillot et al. (Colloid Polym Sci, 2000, Vol. 278, p.74-79).

Claims 15 and 27 are drawn to a method of preparing an IPN comprising, providing a first polymer nanoparticles prepared by mixing first monomer, a surfactant, a first cross linking agent, and first initiator at a first temperature, adding to the first mono-dispersed polymer nanoparticles a second monomer, a second cross linking agent, a second initiator and an activator, mixing the nanoparticles solution for a period of time at a second temperature, isolating the IPN nanoparticles, and the second temperature is about 70ºC.

Cai et al. teach a method of preparing monolithic bulk hydrogels with microstructure (BHM) and a method of forming an interpenetrating polymer network (or IPN) (p.173 Figure 2. and 1st column lines), comprising, synthesizing microgel particles (providing a dispersion of first polymer nanoparticles) by mixing a first monomers poly(-N-isopropylacrylamide) (NIPAAm) and acrylic acid (AA) in appropriate molar ratios without a surfactant, a cross linking agent BIS (or N, N'-methylenebisacrylamide), the solution was purged under N_2 for half an hour, the initiator APS (potassium persulfate) was added and the reaction temperature was maintained 65ºC temperature (at about 70°C), the reactions were allowed to proceed for 6 to 8 hours and the mixture is kept overnight at room temperature for completion of the reaction (p.171 1st column last paragraph and 2nd column 1st paragraph). Cai et al. further teach the NIPAAm monomer, microgel solution, and cross linker BIS were mixed in a bottle, the solution

were shaken for 20 minutes fro complete dissolution of the monomers and then purged with N_2 for 20 minutes for the removal of the oxygen then the initiators APS and SBS (second initiator) were added to the reaction mixture and polymerized at room temperature (at about 21°C) for 24 hours reaction, formed bulk hydrogels were cut and washed to remove unreacted monomer (isolating the hydrogels), (p.171 1st 2nd column 2nd paragraph). Cai et al. teach surfactant free emulsion polymerization (p.171 last paragraph).

Cai et al. do not teach a surfactant. However, Soane teaches a surfactant such as SDS can be used to stabilize the dispersion (column 7 lines 10-11).

Therefore, a person of ordinary skill in the art at the time the invention was made could have been motivated to use a surfactant is the method as taught by Cai et al. with predictable results. The motivation as taught by Soane could be to stabilize the dispersion.

Claims 29-40 and 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cai et al. (Journal of Applied Polymer Science, 2002, Vol. 83, p.169-178) in view of Hennink & Nostrum (Advanced Drug Delivery Reviews, 2002, Vol. 54, p.13-36).

Claims 29-40 are drawn to a method of preparing a nanocluster of cross-linked IPN nanoparticles comprising, providing a dispersion of IPN nanoparticles, adding a first cross linking agent and a second cross linking agent to the dispersion of the IPN nanoparticles, heating the IPN cross linking solution to a first temperature for a period of

time, wherein the IPN nanoparticles have uniformed size and comprise a first polymer network interpenetrating a second polymer network, mixing the nanocluster of cross-linked IPNs with a biologically active material at a second temperature, the first polymer comprises of poly(-N-isopropylacrylamide) and the second polymer comprises poly(acrylic acid), first cross-linking agent comprises EDAC and second cross linking agent comprises adipic acid dihydrazide, heating at a first temperature, about 44°C, for about 25-45 min (33-37 min), mixing cross-linked IPNs with a biologically active material at about 33°C, and hydrodynamic radius in the range from 225 nm to about 240 nm.

Claims 41-47 are drawn to a nanocluster of cross-linked IPN nanoparticles comprising: at least two IPN nanoparticles linked by a cross-linking group, a first polymer network interpenetrating a second polymer network, the cross linking group is adipic acid dihydrazide, wherein each IPN nanoparticles have a uniformed sized and an have an average hydrodynamic radius of nanoparticles is in the range of 155 nm to about 1000 nm.

Cai et al. teach a method of preparing a nanocluster of cross-linked IPN nanoparticles (formation of BHM) comprising, providing a dispersion of IPN nanoparticles, adding a cross linking agent to the dispersion of the IPN nanoparticles, heating the IPN cross linking solution to a first temperature for a period of time, wherein the IPN nanoparticles have uniformed size and comprise a first polymer network interpenetrating a second polymer network, the first polymer comprises of poly(-N-isopropylacrylamide) and the second polymer comprises poly(acrylic acid) (p.171 2nd column 3rd paragraph and p.173 2nd column lines 12-17). Cai et al. teach a nanocluster

of cross-linked IPN nanoparticles comprising: at least two IPN nanoparticles linked by a cross-linking group, a first polymer network interpenetrating a second polymer network (p.173 Figure 2.),

Cai et al. teach among stimuli sensitive hydrogels, poly(-N-isopropylacrylamide) (NIPAAm) is the most widely studied thermosensitive hydrogel, it undergoes a reversible volume phase transition at 32ºC (lower critical solution temperature or LCST)(p.169 1st column lines 10-14). Cai et al. teach the microgel particles (500 to 700 nm) are ionic particles because of the carboxylic charge on acrylic acid (AA), in these microgel particles the AA groups tend to lie on the surface of the particles, and NIPAAm groups lie toward the inside, this prevents aggregation between microgel particles and makes the microgel particles stable in the aqueous solutions. In this conformation, the carboxyl groups of on the microgel particle surface can also be further cross-linked under suitable conditions, forming interpenetrating network structure (or IPN) (p.172 2nd column last paragraph and p.173 1st column). Cai et al. teach when monomer NIPAAm is mixed with the NIPAAm-AA microgel solution and crosslinker, the ionic microgel particles can be crosslinked with one another and into the bulk matrix, forming a BHM (p.173 2nd column and Figure 2.). Cai et al. also teach hydrogels that have micrometer-level dimensions, show promise in pharmaceutical applications, the microgel particles have diameters ranging from 50 nm to 5 μm. Cai et al. teach the properties of two or more bulk hydrogels can be combined by forming interpenetrating polymer networks (IPNs), especially combining the pH and temperature sensitivities. Inside IPN hydrogels, each network may retain its own properties, whereas the proportions of the networks

are varied independently. The combined properties of the IPNs can be controlled by the ratios of their component monomers (p.170, 2nd column 2nd paragraph). Cai et al. further teach mixing the isolated IPN with a biologically active (bovine serum albumin, a protein) material at different temperatures (p.172, 2nd column 1st paragraph). Cai et al. further teach to increase the volume and surface area of the bulk hydrogels, hydrogels can be synthesized at temperatures above the LCST of the polymer by heating the reaction near the end of the polymerization (p.169 2nd column last paragraph).

Cai et al. do not teach the first cross-linking agent comprises EDAC and second cross linking agent comprises adipic acid dihydrazide, heating at a first temperature about 44°C, for about 25-45 min (33-37 min). However, Hennink & Nostrum teach EDC or EDAC, a highly efficient reagent to crosslink water-soluble polymers with amide bonds, and adipic acid dihydrazide, a less toxic cross linking agent for aldehyde-mediated crosslinking of polymers (p.20 1st column 2nd paragraph), (p.19, 1st column lines 20-23). Hennink & Nostrum teach the swelling and degradation of the gels could be controlled by the amount of adipic acid dihydrazide.

Moreover, routine experimentation is widely used by one of ordinary skill in the art to determine optimum or workable ranges of particular parameters such as temperature, time, and the type and amount of cross linking agent in a polymerization reaction. "[W] here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (MPEP Chapter 2100 – p.141).

Therefore, a person of ordinary skill in the art at the time the invention was made could have been motivated to combine the prior art teachings and to modify the method as taught by Cai et al. by substituting the cross linking agent with the cross linking agents as taught by Hennink & Nostrum with predictable results. The claim method would have been obvious because substitution of one known crosslinking agent with another would have yielded predictable results to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on 9:00 am to 5:30 pm EST Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

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